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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US90/01275 <b>(22) International Filing Date:</b> 8 March 1990 (08.03.90)  <b>(30) Priority data:</b> 320,944                      9 March 1989 (09.03.89)                      US  <b>(71) Applicant:</b> MICRO VESICULAR SYSTEMS, INC. [US/ US]; 22 Cotton Road, Suite 230, Nashua, NH 03063 (US).  <b>(72) Inventor:</b> WALLACH, Donald, F., H. ; 94 Dow Road, Hol- lis, NH 03049 (US).  <b>(74) Agents:</b> LOREN, Ralph, A. et al.; Lahive & Cockfield, 60 State Street, Boston, MA 02109 (US).		<b>(81) Designated States:</b> AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (Eu- ropean patent), FI, FR (European patent), GB (Euro- pean patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, MW, NL (Euro- pean patent), NO, RO, SD, SE (European patent), SU.  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
<b>(54) Title:</b> BIODEGRADABLE SUPERABSORBING SPONGE  <b>(57) Abstract</b>  A new superabsorber which gels and cross-links as hydrated has been developed. The superabsorber contains a branched-chain polyanionic carbohydrate such as carboxymethylcellulose, a cross-linking agent, and a hydrophobic carboxylic acid. The superabsorber is biodegradable and non-toxic.		

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BIODEGRADABLE SUPERABSORBING SPONGEBackground of the Invention

The present invention relates to biodegradable gels which act as superabsorbing  
5 sponges. More particularly, the gel of the invention has as high, or higher, liquid and saline uptake than the polyacrylate superabsorbers now being used while having the advantage of being completely biodegradable.

10 Biodegradability has become a necessity in society in the last few years. As more and more products are made disposable, the waste problems associated with these disposables have become increasingly important. One example of this is the  
15 disposable diaper field. Until a few years ago, disposable diapers, though convenient, had not received widespread use because the amount of liquid which could be absorbed was limited. This limitation lead to use of the diapers for extraordinary  
20 circumstances but they were not feasible for most people on a day-to-day basis because of the leakage and resulting diaper rash problem. In order to solve these problems, the diaper manufacturers first used very thick diapers, placing large amounts of fiber  
25 such as cellulose in the diaper to act as a liquid, primarily saline and urine, absorber. These bulky diapers still had limitations on the amount of

liquids they could retain while the bulk made them uncomfortable for the infants to wear.

The first major improvement in the disposable diaper field was the addition of the so-called "superabsorbers" as liquid traps. These superabsorbers are primarily polyacrylate particles which are placed in the diaper in loose form or are entrapped among cellulose fibers. These polyacrylate particles absorb large quantities of water by swelling and acting as individual pseudo-sponges. Since the amount of saline and urine which can be absorbed by these superabsorbers is so much greater than cellulose or other natural fibers, very thin diapers could be used, minimizing the problems to infants and making disposables the diaper of choice. The polyacrylate gel beads move freely relative to each other and form large spaces between each other. However, once fully hydrated, these polyacrylate superabsorbers tend to clump, causing a lumpy diaper and discomfort to the infant.

In addition to the use in diapers, the superabsorbers have other uses. Many other items which are used for absorption of liquid are a fertile ground for use of the superabsorbers. However, the polyacrylate superabsorbers have one major disadvantage; they are not biodegradable. This means that the diapers and all other products made using these superabsorbers are not degraded for decades; in fact, they need hundreds of years to breakdown. This leads to the aforementioned waste problem. Another disadvantage of the polyacrylates is that they absorb

maximally at 0% saline while urine and most body fluids are about 0.15 N saline.

Materials which absorb liquid and are biodegradable such as those of the present invention  
5 have other possible uses as well. The entrapment of particles, including macromolecules such as hemoglobin and cells such as erythrocytes, is particularly important for feminine napkins and similar products. Superabsorbers have not made a  
10 great dent in this field even though they have the necessary liquid absorption because they cannot entrap large particulates.

Another possible use for a biodegradable material which will entrap liquid and/or particles is  
15 as a sustained release vehicle. In certain instances, the molecules to be delivered can be part of the structural material of the sponge itself. Most materials which are presently being tested as sustained release vehicles, e.g., microcapsules,  
20 liposomes and related capsular type products, have substantial costs and time associated with their manufacture. The ability to make a product in situ, apply it to a given area, and then let it degrade under ordinary conditions to release entrapped  
25 material, would solve many problems.

A further use of a gel which entraps liquids and particles is as a biological protective barrier. For example, a gel which entraps bacteria as it is hydrated, or prevents their passage once formed, can  
30 be used as a wound dressing, protecting the wound

from bacteria while allowing air flow and/or free flow of liquid to the injury. A further use is in a diaper where coliform bacteria can breakdown urea in urine to ammonia, changing the pH and promoting  
5 diaper rash.

Accordingly, an object of the invention is to provide a biodegradable material that has high uptake for water and saline.

Another object of the invention is to  
10 provide a biodegradable carrier or sustained release delivery system for drugs and other molecules.

A further object of the invention is to provide a material and method for entrapment of particulates such as erythrocytes and protein  
15 molecules such as hemoglobin.

A still further object of the invention is to provide a protective barrier which prevents the passage of particles such as bacteria or macromolecules, e.g., for use as a wound bandage.

20 These and other objects and features of the invention will be apparent from the following description.

#### Summary of the Invention

The present invention features a composition  
25 of matter which acts as a synthetic sponge as well as methods of absorbing aqueous or saline solutions.

The invention further features methods of entrapping particles in a gel. The gel-like composition of matter can be used as a protective barrier and as a sustained release vehicle which releases entrapped particles or molecules such as drugs over time.

In brief, a composition of matter has been developed which acts as a synthetic sponge when allowed to hydrate. A high molecular weight, complex carbohydrate with multiple anion-terminated branches and a cross-linking agent are blended under substantially anhydrous conditions, preferably with a carboxylic acid with a substantial hydrophobic region. Preferred carboxylic acids with substantial hydrophobic regions are fatty acids selected from a group consisting of lauric acid, palmitic acid, oleic acid, stearic acid, benzoic acid, or mixtures thereof. A substantial hydrophobic region means and implies a region with a substantial hydrocarbon chain or ring structure. Preferred branch complex carbohydrates include carboxymethylcellulose, and chemical analogues thereof. Linear complex carbohydrates such as cellulose, gum xanthan, gum karaya, or alginic acid may also be included.

Once the components are intimately blended, e.g., milled together, the components of the mixture can be hydrated and cross-linked substantially simultaneously when in the presence of the hydrating solution. Any of the components may be premixed together or impregnated with one another. In addition, the other reactants may be derivatized with the complex or linear carbohydrates using an



isopropoxide or other similar reaction. Some or all of the fatty acid can be replaced with a "functional fatty acid" or a long-chain carboxylic acid. As used herein, the term "functional fatty acid" means, 5 includes and defines a molecule having a terminal carboxylic acid, a substantial aliphatic portion, and a biological function other than as a breakdown product or precursor in the food chain. Functional fatty acids include acids such as undecylenic acid, 10 arachidonic acid, prostaglandins, prostacyclins, thromboxanes, and their derivatives, chemical analogues and precursors.

As noted, the composition of matter of the invention includes a cross-linking agent as an 15 essential component. The preferred cross-linking agents are metallo-organic compounds of multivalent metals. Organic cross-linking agents such as chitosan, Poly-Cup, chymene, and jeffamine may be used, but are less efficient than the metallo-organic 20 complexes. Oxytetracycline is a highly effective cross-linking agent but has limited application because of its biological activity. Although bivalent molecules such as calcium might be used in certain circumstances, the multivalent metals 25 (valence 3 and over) such as aluminum or chromium are preferred. For many applications aluminum in the form of hydroxy-aluminum diacetate, borate-stabilized dihydroxy-aluminum acetate and/or aluminum sulfate/citrate, may be satisfactory. A most 30 preferred cross-linking agent providing superior performance is an aluminum metallo-organic complex of the hydroxy-aluminum/hydrophobic carboxylate form

such as hydroxy-aluminum benzoate. This agent can act as both the hydrophobic carboxylic acid and the cross-linking agent in a single molecule. Other hydrophobic carboxylic acids such as laurate, 5 stearate, oleate or benzoate can also be used in the metallo-organic complex.

The invention further features a method of absorbing aqueous or saline solutions using the biodegradable synthetic sponge composition of the 10 invention. The synthetic sponge composition is provided in a substantially unhydrated form, for example, by blending the components together to obtain particles of the desired size, and then the solution is absorbed by contacting the solution with 15 the synthetic sponge composition. The synthetic sponge composition hydrates to absorb the solution and substantially simultaneously cross-links into a gel which binds the solution.

The same basic material may be used to 20 encapsulate particles in a gel. The synthetic sponge composition is provided in a substantially unhydrated form and a solution containing the particles to be entrapped within the gel is mixed with the composition. The gel forms by cross-linking, 25 absorbing the liquid and entrapping the particles within the gel. Particles which can be entrapped in this way include macromolecules or proteins such as hemoglobin, bacteria, or cells such as erythrocytes.

Substantially the same entrapment procedure 30 can be used to create a sustained release vehicle.

For example, gels cross-linked by oxytetracycline can be used as a sustained release vehicle for this drug. Many positively charged drugs can be held in polyanionic gels for sustained release. By modifying  
5 the ratios of the different components, and selecting the specific materials which make up the gel, the stability, absorption levels, and firmness of the gel can be modified. For example, changing the fatty acid/carbohydrate ratio can dramatically change the  
10 absorption, and the subsequent release rate, of liquid from the gel. Further, the addition of other materials to the gel, e.g., surfactants such as polyoxyethylene fatty acid ethers or spacers such as silica or clays, can change the properties of the  
15 gel. This change of properties is more clearly explained in the description and the Examples.

#### Detailed Description of the Invention

The hydrated gel described herein is formed by the simultaneous hydration and cross-linking by a  
20 cross-linking agent of polyanionic carbohydrates, preferably together with hydrophobic carboxylates. In contrast to the polyacrylate superabsorbers, which necessarily form discrete particles (as do covalently cross-linked molecules such as cross-linked  
25 carboxymethylcellulose, gelatins, and alginates), the material of the present invention exists in uncross-linked form prior to hydration. Upon hydration, the material forms extend, water-binding networks of biodegradable carbohydrate polymer,  
30 preferably further cross-linked with extended multilamellar sheets of degradable, anionic lipid.

Macroscopically, the gels are stable and can extend several centimeters in several directions upon hydration. These gels can also be formed into a variety of geometries such as rods, disks, and  
5 slabs. The consistency of the gel, and the amount of liquid absorbed, can be changed by modifying the initial composition. In addition, a partially hydrated gel can be further hydrated at a later time by absorption of more liquid.

10           The capacity for uptake of liquid of the compositions of the present invention furthermore depends on the ratio of active acid, e.g., lipids, to active carbohydrate. At low lipid/carbohydrate ratios (on a weight basis), e.g., a 0.1 - 0.2 ratio,  
15 high fluid absorption is observed. In fact, as may be seen from the following Examples, the uptake of 0.15 N saline is considerably greater than that of the polyacrylate superabsorbers. When the ratio of fatty acid to carbohydrate is much higher, e.g.,  
20 approximately 1, the gels do not absorb as much liquid, give up the liquid easier, and act as better delivery systems.

          Functional fatty acids can be used to replace some or all of the fatty acid. The major  
25 advantage of using these functional fatty acids is that as the gels are degraded, the functional fatty acid is released. This acts as a type of delivery system which can have a much higher concentration of the material to be delivered than could be possible  
30 in another type of encapsulation or entrapment system. In fact, a certain proportion of the fatty

acid can be replaced by any carboxyl terminated molecule.

Although branched complex carbohydrates are necessary for practice of the invention, some of these branched carbohydrate fractions can be replaced by linear carbohydrates such as cellulose. The addition of these linear carbohydrates appears to improve the absorption capability of the system, acting synergistically with the other components. Other linear carbohydrates which have been shown to be effective include carbohydrates with terminal glucuronic acid such as alginic acid, gum xanthan and gum karaya. Non-cross-linkable soluble carboxylic acids do not appear to work.

The following Examples will more clearly explain the procedures and processes of the present invention.

Example 1.

This Example shows the fluid uptake of saline for a composition of the invention with low lipid/carbohydrate ratio under pressure conditions designed for testing polyacrylate superabsorbers. Approximately 0.05 g (0.2 mmol) of palmitic acid was blended with 0.5 g carboxymethylcellulose and 0.02 g (0.14 mmol) borate-stabilized dihydroxy aluminum acetate and 1.5 g of cellulose fiber. Blending took place at room temperature by mixing the materials together until they were uniformly blended. The materials were then milled into 500 micron particles.

In a parallel experiment, a high lipid/carbohydrate material was made and tested under the same conditions. This high ratio material is made by blending 1 g of palmitic acid with 1 g of 5 carboxymethylcellulose and 0.04 g of the borate-stabilized dihydroxy aluminum acetate complex. Small portions of the sample (approximately 0.1 g) were blended with 0.5 g of cellulose fiber.

The two samples were tested under the same 10 procedure, as was a polyacrylate superabsorber. The test procedure hydrated the materials by capillary action with 0.15 M NaCl under applied load of 0.22 lbs./in<sup>2</sup> for sixty minutes at room temperature. The amount of fluid take up was then determined 15 gravimetrically. The data shown in all the Tables of Examples show the amount of fluid uptake for the synthetic sponge, determined by correcting for the amount of fluid taken up by the cellulose alone which was determined separately.

20

TABLE 1

<u>System</u>	<u>Fluid Uptake (ml/g)</u>
Low Lipid/Carbohydrate	37.3
High Lipid/Carbohydrate	21.1
Superabsorber	30.4

25

Table 1 shows that the fluid uptake for the low lipid/carbohydrate ratio, in ml of liquid/g of absorber, is higher than the superabsorber while a

lower amount, but still significant, is absorbed by the high lipid/carbohydrate ratio material. This shows that a simple modification of ratios, using exactly the same materials, can lead to a control in  
5 the amount of liquid taken up by the gel.

Example 2.

In this Example, a different test was used to determine fluid retention by two different gels of the invention and a polyacrylate superabsorber. The  
10 first gel, a low lipid/carbohydrate ratio gel, was made by blending 0.05 g palmitic acid with 0.5 g carboxymethylcellulose and 0.02 g of the borate-stabilized dihydroxy aluminum acetate complex. Approximately 0.3 g of this mixture was  
15 then blended with 1.5 g of cellulose fiber.

The second gel of the invention was made by blending 1.0 g of palmitic acid with 1.0 g of carboxymethylcellulose and 0.04 g of the borate-stabilized dihydroxy aluminum acetate  
20 complex. Again, 0.3 g of this mixture was blended with 0.5 g of cellulose fiber.

Samples of each of the two compositions of the invention and a superabsorber (0.3 g each) were sealed in tea bags and immersed in 0.15 N saline for  
25 thirty minutes at room temperature. After removal from the saline, the tea bags were centrifuged at 300 X g for thirty minutes and the amount of saline retained within the material was determined gravimetrically. Again, there was a correction made

for the excess cellulose. Table 2 shows the results of this testing.

TABLE 2

<u>System</u>	<u>Fluid Retention (ml/g)</u>
5 Low Lipid/Carbohydrate	43.0
High Lipid/Carbohydrate	21.1
Superabsorber	36.5

As is clear, the low lipid/carbohydrate ratio material had a greater fluid retention than the  
10 superabsorber while the high lipid/carbohydrate ratio material had a lower retention.

Example 3.

In this series of experiments, the retention of particulate material by the gels of the invention  
15 were tested. In each experiment, 1.0 g of palmitic acid was uniformly blended with 1.0 g of carboxymethylcellulose and 0.04 g of the borate-stabilized dihydroxy aluminum acetate complex, making a high ratio gel. About 0.5 g of the mixture  
20 was hydrated with 25 ml of the test suspension. In the first test, the hydration material was a suspension of human red cells in 0.15 N saline. The gelation occurred within thirty minutes. After two hours, the resulting gel was centrifugally washed  
25 with five volumes of 20% dextran (140,000 Mol. Wt.) dissolved in 0.15 N saline. Each wash had the sample centrifuged for thirty minutes at 3,000 rpm in a



Beckman centrifuge. The red cell-containing gel contracted and floated to the top half of the centrifuge tube while there was substantially no release of red cells. If the cells had been free, they would pellet at the bottom of the centrifuge tube. This shows the retention of the particulate matter, in particular erythrocytes, by the gel of the invention. Over 99% of the cells were contained within the gel, as determined spectrophotometrically. This was true for red cell suspension of 2.5-12.5 times the mixture amount used. In a similar experiment with heparin-treated whole blood, the gel was able to absorb 20 times its weight with similar retention characteristics.

Similar experiments were carried out replacing the red cell suspension with a solution of human hemoglobin in normal saline. Gelation lead to complete incorporation of the hemoglobin solution. After standing for two days, the gel was centrifugally washed five times at the 3,000 rpm for thirty minutes in the Beckman centrifuge in a dextran gradient. Only traces of hemoglobin were observed released into the dextran barrier while substantially all of the rest of the hemoglobin was retained within the gel. By spectrophotographics measurement, about 88% of the hemoglobin was retained.

A further experiment was carried out using the same procedure but replacing the red cell suspension with a suspension of paucilamellar lipid vesicles, made using the materials and procedures described in United States Patent Application Serial

No. 157,571, with an average diameter of about 0.5  $\mu$ . These vesicles had an oil-based center with the liposoluble red dye "Oil Red O" incorporated in the oil as a marker. Gelation in the presence of the vesicles lead to complete incorporation of the vesicles. Over two days, five centrifugal washings of the gels showed a gradual release of the dye-containing vesicles without fractionation or breakdown of the vesicles. This shows that this type of gel could be used as a sustained release vehicle, or that it can act as a protective barrier to large particles. Other paucilamellar lipid vesicles have also been encapsulated.

#### Example 4.

In this experiment, the same high lipid/carbohydrate ratio gel as used in Example 3 was used to show the effects of isotonic changes and permeability of small particles. The gel was manufactured as described above and was hydrated with 25 ml of plain water. The gel was then soaked alternately in several changes of 0.5 ml of 1 M sucrose then water.

The shifts from the hypertonic to hypotonic medium and back caused only transient changes in gel volume at the time of the change of the medium, indicating free permeability of the gels to sucrose. Therefore, it is expected that the gels would also be permeable to molecules of approximately the same size as sucrose including many drugs. Accordingly, the gels could be used as a wound bandage which allows

passage of a drug through the gel to where it is necessary but protection against large particulate-type matter such as bacterial cells. In contrast, exposure of gels to a 20% solution of high molecular weight dextran (140,000 Mol. Wt.) causes reversible shrinking, suggesting that these molecules do not penetrate the gels and cause osmotic loss of water from the gels.

Example 5.

10           In this Example, a functional fatty acid, undecylenic acid, is used in place of a standard fatty acid in forming the gel of the invention. This functional fatty acid is a potent fungicide.

15           To make this gel, 1.0 g of undecylenic acid was uniformly blended with 1.0 g of carboxymethylcellulose and 0.036 g of the borate-stabilized aluminum acetate complex. The sample was hydrated by mixing 25 ml of water with 0.5 g of the mixture. Hydration was complete within 20 thirty minutes, forming a soft gel. The gel slowly releases the undecylenic acid over time. A more rigid gel can be formed by using blends of the functional fatty acid with palmitic or stearic acid.

25           The soft gel is slightly turbid, spreads easily, and sticks to the skin. Because of this, a bandage or wound covering of the undecylenic acid gel could be applied to the skin, providing fungicidal benefits as well as protection against particulate bacteria and infection.

Example 6.

In this Example, two different metallo-organic complexes useful as cross-linking agents within the scope of the invention were made.

- 5 The first, a palmitate-based aluminum metallo-organic complex (PX-L), is made by mixing 0.64 g palmitic acid (0.25 mmol) dissolved in 5 ml of ethanol with 1.4 g (10 mmol) aluminum monoacetate stabilized with boric acid in 5 ml of water. An opalescent solution  
10 resulted. This opalescent suspension can be mixed with carboxymethylcellulose (CMC), with or without cellulose fiber, to provide a cross-linking agent impregnated in the CMC. This same procedure may be used with equal molar amounts of lauric or stearic  
15 acid to form similar complexes.

- To form an benzoate-based aluminum metallo-organic complex (BX-L), a more dilute solution is used. Specifically, 0.61 g of benzoic acid (0.50 mmol) was dissolved in 7.5 ml of ethanol.  
20 The benzoic acid solution was mixed with a solution containing 1.4 g (10 mmol) aluminum monoacetate stabilized with boric acid in 7.5 ml of water. Again, an opalescent suspension resulted. This cross-linking agent can also be impregnated into or  
25 derivatized with CMC or cellulose fiber.

Example 7.

In this Example, the organo-metallic cross-linking agents formed in Example 6 were used to form the sponge-like material of the invention. In

the first such test, 0.2 g of carboxymethylcellulose (CMC), 0.04 g of palmitic acid (PA), 0.2 ml of the benzoate-based aluminum metallo-organic cross-linking agent (BX-L) made in Example 6, and 50 ml of 0.15 N saline were blended. As one of the two variations of the experiment, 0.6 g of cellulose was also used.

The mixture was hydrated by thirty seconds of magnetic stirring and the still-liquid mixture was transferred to 50 ml centrifuge tubes and centrifuged at 300 X g for thirty minutes. At the end of the thirty minute centrifuge period, any free fluid was collected by filtration through a 150  $\mu$  pore size nylon mesh. Highly cohesive, firm gels form within the thirty minute centrifugation.

Retention of liquid was measured at least twenty-four hours after formation. Gel piece aliquots were cut out, weighed, and placed in a centrifuge tube insert, closed its bottom by a perforated screen supporting a piece of non-woven tea-bag paper. After centrifugation at 300 X g for thirty minutes, the amount of liquid released from the gel was determined gravimetrically. Table 3 shows the results of this testing for the material of the invention (CMC/PA/BX-L), with or without cellulose. The same test was carried out using a similar amount of Sanwet IM1500 U.S., a polyacrylic superabsorber, as a control. All values with cellulose are corrected to non-cellulose activities in this and the following Examples.

TABLE 3

<u>System</u>	<u>Absorption (ml/g)</u>
CMC/Palmitate/Benzoate X-link	162 $\pm$ 10
+Cellulose	201 $\pm$ 4
5 Polyacrylic Superabsorber	60 $\pm$ 1
+Cellulose	70 $\pm$ 1

As can be seen from the results of Table 3, the composition of the invention, either with or without cellulose, clearly is superior to the  
10 polyacrylic superabsorbers in terms of retention of 0.15 N saline.

The identical experiment was performed using a composition of the invention which had the palmitate-based cross-linking agent (PX-L) in place  
15 of the benzoate-based cross-linking agent (BX-L). Table 4 shows the results of this experiment, again compared to the superabsorber results.

TABLE 4

<u>System</u>	<u>Absorption (ml/g)</u>
20 CMC/Palmitate/Palmitate X-link	207 $\pm$ 1
+Cellulose	205 $\pm$ 1
Polyacrylic Superabsorber	60 $\pm$ 1
+Cellulose	70 $\pm$ 1

Example 8.

In this Example, a 20% whole blood solution was tested for absorption by a composition of the invention made with the benzoate-based cross-linking agent (BX-L) of Example 6. The composition was made by mixing 0.2 g of carboxymethylcellulose, 0.04 g of palmitic acid, 50 ml of 20% whole blood, 0.15 N saline and 1 ml of the cross-linking agent. Again, the material was tested with and without 0.6 g of cellulose. After hydration, the still-liquid mix was divided into two 25 ml portions, these were transferred to 50 ml centrifuge tubes, and gelation was allowed to proceed under centrifugation at 300 X g (average 4800 lbs./in<sup>2</sup>) for thirty minutes. At the end of the centrifugation, any free fluid was collected by filtration through 150  $\mu$  pore size nylon mesh. Table 5 shows the results of this test. The value without the cellulose is equivalent to an absorption of 35 ml of whole blood, while the cellulose added value is even higher.

TABLE 5

<u>System</u>	<u>Absorption (ml/g)</u>
CMC/Palmitate/Benzoate X-link	175 $\pm$ 1
+Cellulose	223 $\pm$ 1

25 Example 9.

In this Example, undecylenic acid is incorporated into a gel containing the benzoate-based

aluminum metallo-organic complex of Example 6.

Approximately 0.5 ml of the cross-linking complex was combined with 0.5 ml carboxymethylcellulose and 0.5 g of undecylenic acid. The material was hydrated with 5 70 ml with deionized water. A high cohesive but mobile gel formed within thirty minutes. There was no release of water over a period of more than three hours and there was no separation of free undecylenic acid.

10           The same approach could be used to incorporate a variety of carboxyl terminal functional molecules such as prostaglandins, prostacyclins, thromboxanes and their precursors such as arachidonic acid. In addition, certain antibiotics such as 15 oxytetracycline can be used in place of some or all of the cross-linking agents.

          Other materials which could be used to replace part the fatty acid include carboxylic acids, carboxylic peptides, nonionic surfactants, and 20 steroids such as cholesterol or hydrocortisone. Selection of proper acidic constituents can modify gel properties. The steroid can be present in the system up to at least 10% of the fatty acid without disturbing the gel. Therefore, these gels could be 25 used as a delivery systems for a variety of molecules such as steroids.

          In addition, as shown previously, lipid vesicles can be incorporated into the gels as particulate matter. Since these lipid vesicles can 30 also be designed to carry a variety of materials



which could not otherwise be carried in the gel, a wound patch or other covering made of the gel with the vesicles dispersed therein could be used to apply drugs on a time-released basis to a selected site.

5           Those skilled in the art will be able to determine other modifications of the exemplary procedures and materials. Such other modifications are within the scope of the following claims.

What is claimed is:

1. A composition of matter which acts as a synthetic sponge when allowed to hydrate comprising a non-hydrated mixture of:

a carboxylic acid with a substantial  
5 hydrophobic region; and

a branched complex carbohydrate;

whereby said composition can be hydrated and cross-linked simultaneously in the presence of a hydrating solution.

10 2. The composition of claim 1 further comprising a separate cross-linking agent.

3. The composition of claim 1 wherein said carboxylic acid comprises a fatty acid.

4. The composition of claim 3 wherein said  
15 fatty acid is selected from the group consisting of lauric acid, palmitic acid, stearic acid, oleic acid, benzoic acid, and mixtures thereof.

5. The composition of claim 1 wherein said carboxylic acid comprises a functional fatty acid.

20 6. The composition of claim 5 wherein said functional fatty acid is selected from the group consisting of undecylenic acid, arachidonic acid, prostaglandins, prostacyclins, thromboxanes, and their derivatives, chemical analogues, and precursors.

7. The composition of claim 1 wherein said branched complex carbohydrate is selected from the group consisting of carboxymethylcellulose, chitosan, and their derivatives and chemical analogues.

5 8. The composition of claim 1 further comprising a linear carbohydrate.

9. The composition of claim 2 wherein said cross-linking agent is a metallo-organic cross-linking agent which includes a multivalent  
10 metal ion.

10. The composition of claim 9 wherein said multivalent metal ion is selected from the group consisting of aluminum ions, chromium ions, and other metal ions with a valence greater than 2.

15 11. The composition of claim 9 wherein said metallo-organic cross-linking agent comprises both said carboxylic acid and said cross-linking agent.

12. The composition of claim 2 wherein said cross-linking agent is an organic cross-linking agent  
20 with an effective valence of at least 3.

13. The composition of claim 2 wherein said fatty acid is selected from the group consisting of lauric, palmitic, oleic, benzoic, and stearic acids, said branched complex carbohydrate is selected from  
25 the group consisting of carboxymethylcellulose, chitosan, and mixtures thereof, and said cross-linking agent is selected from the group

consisting of aluminum acetate, aluminum borate, benzoate-based aluminum metallo-organic complex, palmitate-based aluminum metallo-organic complex, and mixtures thereof.

5 14. A method of absorbing aqueous or saline solution using a biodegradable synthetic sponge composition comprising the steps of:

providing said synthetic sponge composition in a substantially unhydrated form, said synthetic  
10 sponge composition containing a carboxylic acid with a substantial hydrophobic region, and a branched complex carbohydrate;

contacting said solution to be absorbed with said synthetic sponge composition;

15 whereby said synthetic sponge composition hydrates to absorb said solution and cross-links into a gel substantially simultaneously.

15. The method of claim 14 wherein said composition further comprises a separate  
20 cross-linking agent.

16. The method of claim 14 wherein said carboxylic acid comprises a fatty acid.

17. The method of claim 16 wherein said fatty acid is selected from the group consisting of lauric,  
25 palmitic, benzoic, and stearic acids, and mixtures thereof.

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18. The method of claim 14 wherein said branched complex carbohydrate is selected from the group consisting of carboxymethylcellulose, chitosan, and their derivatives and chemical analogues.
- 5 19. The method of claim 14 wherein said composition further comprises a linear carbohydrate.
20. The method of claim 15 wherein said cross-linking agent is selected from a group consisting of metallo-organic complexes containing  
10 aluminum ions, chromium ions, and other metal ions with a valence of at least 3.
21. The method of claim 15 wherein said carboxylic acid and said cross-linking agent comprise the same molecule.
- 15 22. The method of entrapping particles in a gel comprising the steps of:
- providing a synthetic sponge composition in a substantially unhydrated form, said synthetic sponge composition containing a carboxylic acid with  
20 a substantial hydrophobic region, and a branched complex carbohydrate;
- contacting a solution containing said particles to be entrapped with said synthetic sponge composition;
- 25 whereby said gel is formed by the combined hydration and cross-linking of said synthetic sponge composition, thereby entrapping the particles.

23. The method of claim 22 wherein said composition further comprises a separate cross-linking agent.
24. The method of claim 22 wherein said  
5 carboxylic acid comprises a fatty acid.
25. The method of claim 22 wherein said particles to be entrapped are selected from the group consisting of cells, bacteria, and macromolecules.
26. The method of claim 22 wherein said fatty  
10 acid is selected from the group consisting of lauric, palmitic, benzoic, and stearic acids, and mixtures thereof.
27. The method of claim 22 wherein said branched complex carbohydrate is selected from the group  
15 consisting of carboxymethylcellulose, chitosan, and their derivatives and chemical analogues.
28. The method of claim 22 wherein said composition further comprises a linear carbohydrate.
29. The method of claim 23 wherein said  
20 cross-linking agent is selected from the group consisting of metallo-organic complexes containing aluminum ions, chromium ions, and other metal ions with a valence of at least 3.
30. The method of claim 22 wherein said  
25 entrapment acts as a barrier to the passage of said entrapped particles.

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31. The method of claim 22 wherein said entrapped particles are released over time from said gel, whereby said gel acts as a sustained release vehicle.

5 32. The method of claim 23 wherein said carboxylic acid and said cross-linking agent comprise the same molecule.

# INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US90/01275**

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) <sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC  
**INT.CL. <sup>5</sup> A61F 13/15 B01D 15/00 B01J 13/00 B01J 20/22 B01J 20/26 C 09K 3/00**  
**U.S. CL. 134/40,41,42 210/660,767 252/194,315.3 502/404 604/368**

## II. FIELDS SEARCHED

Minimum Documentation Searched <sup>7</sup>

Classification System	Classification Symbols
U.S.	134/40,41,42 210/660,767 252/194,315.3 502/404 604/368

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>

## III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup>

Category <sup>*</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	US, A, 4,786,415 (SHIBATA ET AL) 22 November 1988 see abstract, col. 2, lines 9-23, Synthesis Examples 9 and 11.	1,3-8,14,16-19 22,24-28,30-32
A	US, A, 3,969,280 (SAYCE ET AL) 13 July 1976 see abstract, col.1, lines 49-64, col.2, lines 13-16, the examples.	1-32
A	US, A, 4,090,013 (GANSLOW ET AL) 16 May 1978, see abstract, col. 4, lines 3-10 & 40-49, the examples.	1-32
A	US, A, 4,160,063 (TITUS) 03 July 1979, see abstract, col. 2, lines 23-34, col. 3, lines 17-27.	1-32
A	US, A, 4,454,055 (RICHMAN ET AL) 12 June 1984 see abstract, col. 2, lines 33-49, col. 2, line 59 to col.3, line 2, col. 5, lines 12-38 and the examples.	1-32
A	US, A, 4,486,335 (MAJEWICZ) 04 December 1984, see abstract, col.1, line 67 to col. 2, line 10.	1-32
A	US, A, 4,548,847 (ABERSON ET AL) 22 October 1985,	1-32

<sup>\*</sup> Special categories of cited documents: <sup>10</sup>

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

**13 April 1990**

International Searching Authority

**ISA/US**

Date of Mailing of this International Search Report

**20 JUL 1990**

Signature of Authorized Officer -

**Patrick P. Garvin**



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A,P	US, A, 4,826,880 (LESNIAK ET AL.) 02 May 1989, See col. 3, lines 19-59.	1-32

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	see abstract, col. 1, lines 5-8, col. 2, lines 11-28.	
A	US, A, 4,610,678 (WEISMAN ET AL) 09 September 1986, see col. 4, lines 32-52 and the examples.	1-32
A,P	US, A, 4,812,486 (HOSOKAWA ET AL.) 14 March 1989, See abstract, col. 2, lines 16-26 & 34-53 col. 3, lines 12-21.	1-32
A	CA 1,152,483 (WINDUST) 23 August 1983, see pg. 1, lines 1-8, pg. 3, lines 6-8, pg. 4, lines 7-11, pg. 6 lines 9-11 and the examples.	1-32

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE<sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers \_\_\_\_\_, because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:

2. ☐ Claim numbers \_\_\_\_\_, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out <sup>13</sup>, specifically:

3. ☐ Claim numbers \_\_\_\_\_, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING<sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

(see attached sheet)

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

- I. Claims 1-13, drawn to a composition of matter.
- II. Claims 14-21, drawn to a method for absorbing an aqueous or saline solution
- II. Claims 22-32, drawn to a method for removing particles from a solution

Lack of unity of invention exists since the composition of matter has separate multiple uses which are also claimed.